Emergence of Metronidazole-Resistant *Bacteroides fragilis*, India

To the Editor: Members of the *Bacteroides fragilis* group are the most commonly isolated anaerobic pathogens in humans. Metronidazole has been the drug of choice for preventing and treating such infections for 40 years. Although *B. fragilis* exhibits the broadest spectrum of recognized resistance to antimicrobial agents among anaerobes, the worldwide rate of metronidazole resistance remains low, <5% (1,2). We report here the first metronidazole-resistant strain of *B. fragilis* from India.

A 34-year-old man with myelodysplastic syndrome was admitted to our hospital with a short history of myalgia, general malaise, and bleeding gums. Bone marrow examination showed evidence of severe aplastic anaemia, for which he was treated with cyclophosphamide and blood transfusions. Ceftazidime and amikacin were also administered empirically for febrile neutropenia. The patient remained in the intensive care unit of our medical oncology ward and was given repeated courses of chemotherapy and blood transfusions. He also had repeated episodes of febrile neutropenia, which resolved with a combination of vancomycin, aminoglycosides, and third-generation cephalosporin. After 4 months in the hospital, during an episode of febrile neutropenia, the patient's condition started to deteriorate, and high-grade fever developed. Physical examination showed temperature of 38°C, heart rate 80/min, blood pressure 100/70 mmHg, and marked pallor. Laboratory investigations showed a hemoglobin level of 4g/dL and marked neutropenia (absolute neutrophil count 320/mm^3). Liver and renal function test results were within normal limits. Peripheral blood smears were negative for malarial parasites. Culture of urine revealed no growth, and the Widal test was negative. Two blood samples were collected in Wampole isolator tubes (Wampole Laboratories, Cranbury, NJ), for isolation of aerobic and anaerobic bacteria. Subsequently, intravenous antimicrobial therapy with vancomycin, metronidazole, and ceftazidime was started. The patient died a day after collection of blood for culture.

Antemortem blood cultures grew *Pseudomonas aeruginosa* and *B. fragilis.* The isolate of *B. fragilis* was identified by conventional tests and Rap ID ANA II system (Innovative Diagnostic System, Norcross, GA). *P. aeruginosa* was sensitive to piperacillin but resistant to amikacin, ceftazidime, cefotaxime, and ciprofloxacin. *B. fragilis* was resistant to metronidazole (MICs, 256 µg/mL) by both standard broth dilution method and E-test (AB Biodisk, Solne, Sweden). The isolate was also resistant to cefotaxime and ceftazidime. However, it was sensitive to chloramphenicol, clindamycin, and imipenem.

Primary bacteremia caused by anaerobic organisms accounts for <5% of septicemia in cancer patients (3). Chemotherapy is a known predisposing factor for anaerobic bacteremia because it causes gastrointestinal ulceration, which permits anaerobes to enter circulation (4).

Anaerobic bacteremia is usually polymicrobial in etiology and has a high death rate (4). In this case, both bacterial isolates were resistant to the empirical treatment. Delay in initiating appropriate therapy was perhaps a major contributor to the patient's death.

Metronidazole is the drug of choice for empirical coverage of anaerobic infections. The precise incidence of resistance to metronidazole in *B. fragilis* isolates is difficult to estimate (5), since routine antimicrobial sensitivity testing of anaerobes is not being done by most laboratories in the world. Published articles reveal only a few reported cases of *B. fragilis* that were resistant to metronidazole (6-10). Although the incidence of resistance to penicillin, cephalosporins, and clindamycin is increasing dramatically, no resistance to metronidazole in *B. fragilis* was found in some large-scale studies done throughout the world (11,12).

The true incidence of metronidazole resistance in India too is possibly underestimated since antimicrobial sensitivity testing is not being done routinely. However, we are conducting antimicrobial susceptibility testing of all anaerobic isolates in our institute. In a previous study we conducted (13), contrary to this report, none of 32 clinical isolates belonging to the family *Bacteroidaceae* obtained over a 5-year period were resistant to metronidazole.

Recently, the anaerobic reference unit in the UK noted a possible increase in the incidence of metronidazole resistance in *B. fragilis*, an observation that would have major implications for clinical microbiology laboratories, as well as for prophylactic and treatment regimens (5).

There is now a growing debate whether in vitro susceptibility testing should be performed for all *Bacteroides* isolates to guide antimicrobial therapy. The acquisition of metronidazole resistance by *B. fragilis* reported here from India emphasizes the need for a study to assess more accurately the susceptibilities of clinical isolates of *Bacteroides* spp.

Diagnostic microbiology laboratories and clinicians should be aware that the incidence of metronidazole resistance in clinically significant anaerobes may be increasing (5). Since antimicrobial resistance in anaerobes varies from one hospital to another and between different geographic locations, all hospitals should survey their sensitivity patterns and report any emerging resistance.

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References

1. Finegold SM, Wexler HM. Present status of therapy for anaerobic infections. Clin Infect Dis 1996;23(Suppl 1):S9-14.
2. Falagas ME, Siakavella S. *Bacteroides, Prevotella*, and *Porphyromonas* species. A review of antibiotic resistance and therapeutic options. Int J Antimicrob Agents 2000;15:1-9.
3. Freifeld AG, Walsh TJ, Philip A. Infections in the cancer patient. In: Devita VT Jr, Hellman S, Rosenberg SA, editors. Cancer. Principles and practice of oncology. 5th ed. New York: Lippincott-Raven; 1997. p. 2659-04.
4. Bodey GP. Infections in patients with cancer. In: Holland JF, Frei F, editors. Cancer medicine. 2nd ed. Philadelphia: Lea and Febiger; 1982. p. 1339-72.
5. Brazier JS, Stubbs SL, Duerden BI. Metronidazole resistance among clinical isolates belonging to the *Bacteroides fragilis* group: time to be concerned? J Antimicrob Chemother 1999;44:580-1.
6. O'Donoghue MA, Potter J, Allen KD. Metronidazole-resistant *Bacteroides fragilis* infection. J Infect 1992;25:211-4.
7. Hickey MM, Davies UM, Dave J, Vogler M, Wall R. Metronidazole resistant *Bacteroides fragilis* infection of a prosthetic hip joint. J Infect 1990;20:129-33.

8. Brogan O, Garnett PA, Brow R. *Bacteroides fragilis* resistant to metronidazole, clindamycin and cefoxitin. J Antimicrob Chemother 1989;23:660-2.
9. Lamothe F, Fijalkowski C, Malouin F, Bourgault AM, Delornel L. *B. fragilis* resistant to both metronidazole and imipenem. J Antimicrob Chemother 1986;18:642-3.
10. Turner P, Edward SR, Weston V, Gazes A, Ispaham P, Greenwood D. Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of *Bacteroides fragilis*. Lancet 1995;345:1275-7.
11. Snydman DR, Jocubus NV, Dermott LA, Supran S, Cuchural CG, Finegold S. Multicentric study of in vitro susceptibility of the *Bacteroides fragilis* group 1995 to 1996 with comparison of resistance trends from 1990 to 1996. Antimicrob Agents Chemother 1999;2417-22.
12. Aldridge KE, Gelfand M, Reller LB, Ayers CW, Pierson CL, Schoenknecht F, et al. A five year multicentre study of the susceptibility of the *Bacteroides fragilis* group isolates to cephalosporins, cephamicins, penicillin, clindamycin and metronidazole in the United States. Diagn Microbiol Infect Dis 1994;18:235-41.
13. Chaudhry R, Mishra B, Dhawan B, Sharma N. Anaerobic infections in an Indian tertiary care hospital with special reference to Bacteroidaceae. J Infect 1999;38:54-5.